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ORIGINAL

Effect of kombucha green tea (*Camellia sinensis*) on mRNA SREBP-1c expression of dyslipidemic model rats

Efecto del té verde kombucha (*Camellia sinensis*) sobre expresión ARNm SREBP-1c de ratas modelo dislipidémicas

Linda[1], Lina Lukitasari[2] ✉, Citrawati D.K. Wungu[2,3], Ira Humairah[2], Tri Hartini Yuliawati[4], Sulistiawati[5], Rahmad Darmawan[1]

[1]Universitas Airlangga, Faculty of Medicine, Master of Basic Medical Science. Surabaya, Indonesia
[2]Universitas Airlangga, Department of Physiology and Biochemistry. Surabaya, Indonesia.
[3]Universitas Airlangga, Institute of Tropical Disease (ITD). Surabaya, Indonesia.
[4]Universitas Airlangga, Department of Anatomy, Histology, and Pharmacology. Surabaya, Indonesia.
[5]Universitas Airlangga, Department of Public Health and Preventive Medicine. Surabaya, Indonesia.

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Corresponding author: Lina Lukitasari ✉

ABSTRACT

Introduction: dyslipidemia is a condition marked by irregularities in the levels of lipids in the blood. The long-term use of synthetic hypolipidemic drugs can lead to numerous side effects, necessitating the search for alternative herbal remedies. Potential benefits of kombucha green tea (KGT), a traditional fermented drink with symbiotic SCOBY culture, known for its hypocholesterolemic, hepatoprotective, and antioxidant effects. These properties contribute to the management of advanced dyslipidemia by enhancing the activation of AMPK, which represses transcription of SREBP-1c involved in coding genes related to de novo lipogenesis in the liver. This study aims to investigate the potential benefits of KGT in *Rattus norvegicus* dyslipidemia.
Method: the experiment was conducted on five groups of male *Rattus norvegicus*, including a dyslipidemia control group (DLP), a healthy control group (NC), and the DLP group with KGT intervention at doses of 70, 85, and 100 mg/kg BW. SREBP-1c mRNA expression was analyzed using Real Time-qPCR.
Results: significant decrease in TC, LDL, and TG levels and an increase in HDL between the DLP group and the KGT intervention group ($p<0,05$). Moreover, SREBP-1c mRNA expression also decreased in all KGT treatment groups compared with the DLP group ($p<0,05$).
Conclusions: supplementation KGT in this study was shown to reduce the level of mRNA expression of SREBP-1c in the liver and improve serum lipid profile of dyslipidemic rats.

Keywords: Kombucha Green Tea; SREBP-1c; Dyslipidemia; Polyphenols; Lipids.

RESUMEN

Introducción: dislipidemia una condición caracterizada por irregularidades en los niveles lípidos en la sangre. El uso largo plazo medicamentos hipolipemiantes sintéticos puede provocar numerosos efectos secundarios, lo que hace necesario buscar remedios herbales alternativos. Se destacan los beneficios potenciales del té verde de kombucha (KGT), una bebida fermentada tradicional con cultivo simbiótico SCOBY, conocida por sus efectos hipocolesterolémicos, hepatoprotectores y antioxidantes. Estas propiedades contribuyen manejo la dislipidemia avanzada mejorar la activación AMPK, que reprime la transcripción SREBP-1c, involucrada en

la codificación genes relacionados con la lipogénesis de novo en el hígado. Este estudio tiene como objetivo investigar los beneficios potenciales de KGT en la dislipidemia de Rattus norvegicus.
Método: el experimento se llevó a cabo en cinco grupos de Rattus norvegicus machos, incluyendo un grupo de control de dislipidemia (DLP), un grupo de control saludable (NC) y tres grupos DLP tratados con KGT en dosis de 70, 85 y 100 mg/kg de peso corporal. La expresión de SREBP-1c se analizó utilizando Real Time-qPCR.
Resultados: se produjo un descenso significativo en TC, LDL y TG, junto con un aumento en HDL entre el grupo DLP y el grupo de intervención KGT (p<0,05). Además, la expresión de ARNm SREBP-1c también disminuyó en todos los grupos de intervención KGT con grupo DLP (p<0,05).
Conclusiones: la suplementación con KGT en este estudio mostró reducir el nivel de expresión de ARNm de SREBP-1c en el hígado y mejorar el perfil lipídico en suero de ratas dislipidémicas.

Palabras clave: Té Verde de Kombucha; SREBP-1c; Dislipidemia; Polifenoles; Lípidos.

INTRODUCTION

Statistical data provided by the World Health Organization (WHO) in 2019, cardiovascular diseases result in more than 17,9 million deaths each year.[1] Pathogenesis of atherosclerosis in the walls of blood vessels ultimately leads to coronary heart disease and stroke, primarily caused by dyslipidemia.[2] Dyslipidemia is abnormalities in lipid profile levels in the blood, marked by increased total cholesterol (TC), low density lipoprotein cholesterol (LDL), and triglycerides (TG), with decreased high density lipoprotein cholesterol (HDL) levels.[3]

Synthesis and absorption of cholesterol, fatty acids, and the utilization of glucose in the liver are regulated by Sterol Regulatory Element Binding Protein (SREBP).[4] In contrast, SREBP-1c plays a more specific role in promoting fatty acid synthesis rather than cholesterol production.[5] Excessive expression of SREBP-1c significantly enhances the regulation, activation, and synthesis of fatty acid enzymes such as Acyl CoA Synthetase Long Chain Family Member-1 (ACSL1), Acetyl CoA Carboxylase-1 (ACC1), and Fatty Acid Synthase (FAS), thereby increasing the synthesis and storage of TG. Furthermore, excessive expression of SREBP-1c also inhibits the expression of lipid oxidation genes such as Carnitine Palmitoyltransferase-1 (CPT1) and Carnitine Palmitoyltransferase-2 (CPT2), which play a role in reducing Very Low-Density Lipoprotein (VLDL) synthesis, leading to the accumulation of large amounts of TG in hepatocytes. Additionally, excessive expression of SREBP-1c contributes to insulin resistance by transcriptionally repressing the Insulin Receptor Substrate-1 (IRS-1) gene through phosphorylation of the Sterol Regulatory Element (SRE) promoter in the nucleus.[6,7]

Pharmacological therapy for dyslipidemia, such as long-term use of statin-class hypolipidemic drugs, can lead to several side effects, including hepatotoxicity, malaise, rhabdomyolysis, and myopathy. Due to the numerous side effects associated with these chemical medications, there is a need to explore alternatives in the form of herbal remedies.[8] Kombucha tea is a traditional beverage resulting from the fermentation of a symbiotic culture of bacteria and yeast (SCOBY). Previous research found that the lowest IC50 value contained in kombucha with a substrate of green tea, ranging from 19,76 to 22,74 µg/mL, compared to other types of tea such as black, white, and oolong tea. This proves that the levels and activity of antioxidant compounds in kombucha based on green tea is significantly higher than other types of tea.[9] Based on the above description and the benefits of producing traditional medicine in the form of fermented kombucha drinks, it is necessary to conduct research on the effects of administering kombucha green tea (Camellia sinensis) on serum lipid profile levels and the expression of SREBP-1c transcription factor mRNA in liver tissue using male Rattus norvegicus as a dyslipidemia model. The doses used in this study are 70, 85, and 100 mg/kg BW of kombucha green tea administered for 14 days.

METHOD

Preparation of kombucha green tea

Green tea powder (Herbal Anugrah Alam, Indonesia) and kombucha starter SCOBY (Food Microbiology Laboratory, Universitas Brawijaya, Malang, Indonesia). Preparation of KGT begins by dissolving 12 g of dry green tea powder in distilled water (1000 ml) at 90°C (10 min). Then, 100 grams of sucrose is added and filtered using a Buchner funnel lined with double-layer filter paper. Following this, 100 ml of tea solution and 10% w/v SCOBY cellulose liquid culture are inoculated, covered with cheesecloth, and tied with string, then incubated for 14 days at room temperature in the dark. Production of kombucha fermentation was carried out under laboratory and aseptic condition.[10,11]

Animal Handling and Ethical Approval

Male *Rattus norvegicus* (150-200 grams) (Faculty of Veterinary Medicine, Universitas Airlangga, Indonesia),

were placed at a controlled temperature of 22 ± 2ºC with a light-dark cycle for 12 hours. The mice were divided into two main groups, received standard pellet feed (NC) as the healthy control, and the dyslipidemia control, received a high fat diet (HFD) consisting of a mixture of standard feed with duck egg yolk and quail egg yolk, containing 22,36 % protein, 11,38 % lipid, and 49,57 % carbohydrate, with a total of 3398,6018 kcal/kg (Veterinary Testing and Feed Analysis Unit, Faculty of Veterinary Medicine, Universitas Airlangga, Indonesia). Additionally, they were given packaged Yongs Deli Pork lard oil (Madiun, Indonesia) via oral gavage with dose of 10 ml/kg BW.[12,13] At the 6th week of the dietary protocol, the HFD group of rats was divided into 4 treatment groups: dyslipidemia + distilled water (DLP), dyslipidemia + KGT 70, 85, and 100 mg/kg BW. The administration of kombucha green tea was accompanied by continued feeding of the high-fat diet for 14 consecutive days (figure 1).

All experimental procedures were conducted in accordance with the Guidelines for the Ethical Use of Animals in Applied Etiological Studies and were approved by the Health Research Ethics Committee, Faculty of Medicine, Airlangga University, Indonesia (Number: 41/EC/KEPK/FKUA/2024).

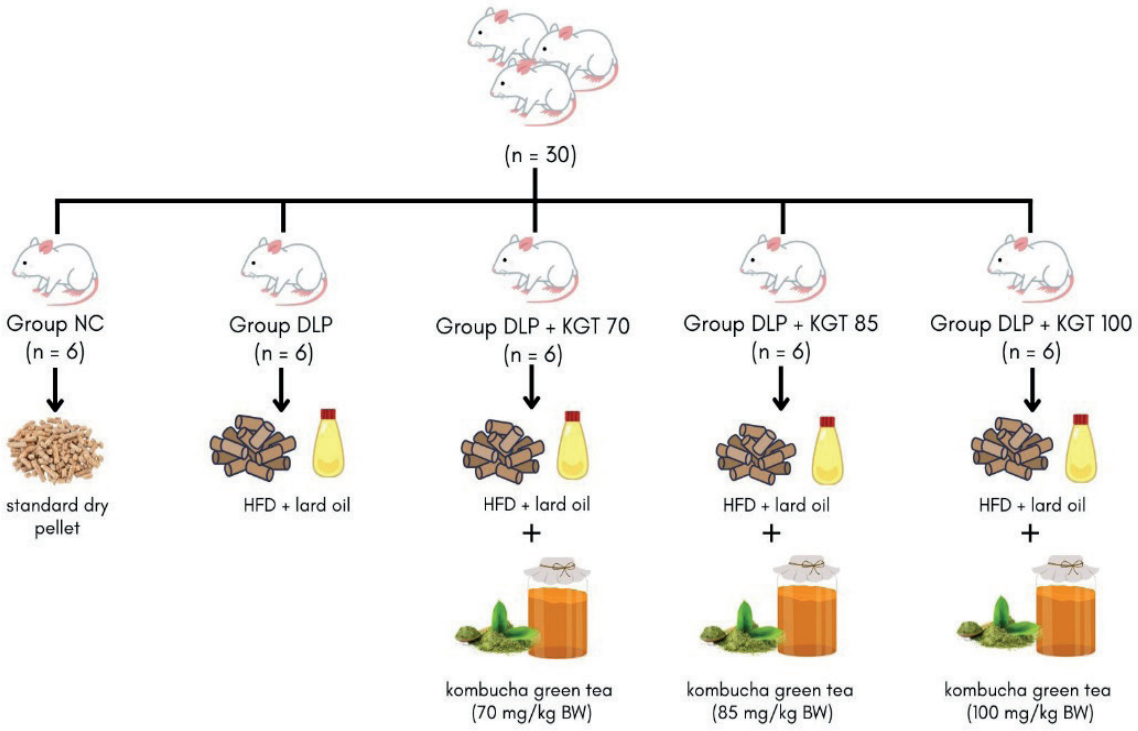

Figure 1. Sample group allocation flow diagram

Phytochemical Testing

Samples of green tea (GT) infusion and KGT were reacted with 0,2 M Folin-Ciocalteu phenol reagent, Na2CO3 5%, $NaNO_2$ 5%, AlCl3 10%, and NaOH 1 M. Phytochemical testing using Shimadzu UV-1800 UV-Vis spectrophotometer (serial No. A116353) at wavelengths of 640 nm and 510 nm.[14,15]

Serum Lipid Profile

Anesthesia was administered using a combination of ketamine and xylazine (1:1). Blood was drawn from the heart and placed into a vacutainer tube without anticoagulant, left at room temperature to clot, then centrifuged at 3000 rpm for 15 minutes to obtain serum.The serum was analyzed using the Automatic Clinical Chemistry Analyzer Erba XL-640, reacting it with Erba Mannheim X SysPack Reagent (Erba Lachema, Czech Republic).

Real Time-PCR

RNA isolation from frozen rat liver tissue was performed using the Biospin Total RNA Extraction KIT II, Cat. No. BSC80S1 (Bioer Technology, China). The total RNA concentration of the samples was measured by observing the 260/280 ratio using a SmartSpec Plus Spectrophotometer to assess RNA purity. Real-Time qPCR analysis using SYBR Green method, employing NEXpro™ 1-Step qRT PCR 2X Master Mix Cat. No. NexQ-7200 (Genes Laboratories, Korea). The measurement process began by preparing the reaction components: 10,0 µL

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of qRT PCR Master Mix, 0,875 µL each of 10 µM forward and reverse primers, 2,0 µL of RNA template, and 6,25 µL of RNase Free Water. The primers used were SREBP-1c and U6 (IDT, San Diego) (table 1), Real Time-PCR measurements were performed using the Biorad CFX 96 RT-qPCR system. The results of the amplification will be normalized using the 2-ΔΔCT method.[16]

Table 1. Primer sequences in rats

Gene Name	Primer (5'-3')	bp
SREBP-1c[30]	Forward TGGACGAGCTGGCCTTCGGT	61
	Reverse GGCCAGCGGCAGGCTAGATG	
U6 (HG)[31]	Forward GCTCGCTTCGGCAGCACA	95
	Reverse AACGCTTCACGAATTTGCGTG	

Note: HG: housekeeping gene; bp: base pair.

Statistical Analysis

To determine whether there was a statistically significant decrease, One-Way ANOVA was used (p<0,05), followed by the Post-Hoc LSD test. The calculations were performed using the IBM SPSS® statistical (version 25).

RESULT

Total Polyphenol and Phenolic Acid Compounds in Green Tea and Kombucha Green Tea

Examination of each component was conducted in triplicate. Based on figure 2, the results of the Unpaired Sample T-Test analysis showed that the levels of phenolic acid compounds (A) and polyphenols (B) KGT is significantly higher (p<0,05) than GT.

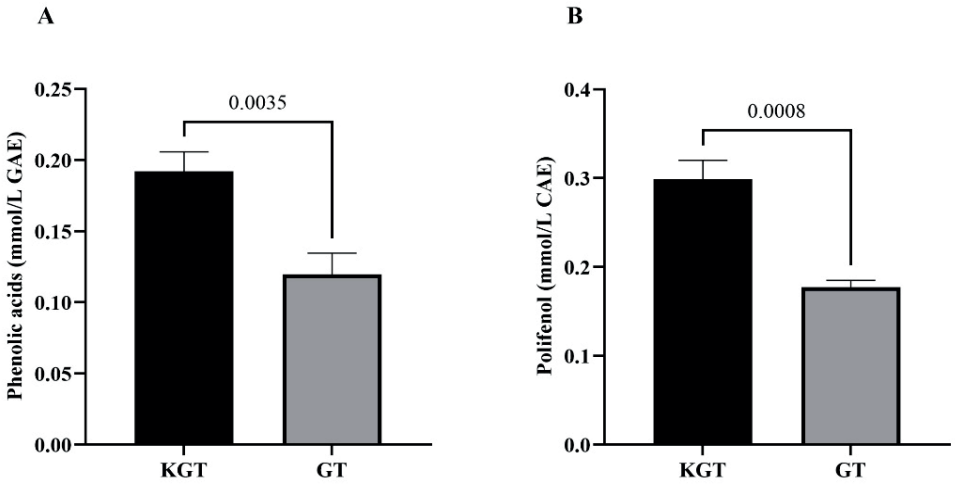

Figure 2. Differences in total levels of phenolic acid compounds (A) and polyphenols (B) in KGT and GT

Note: Data are expressed as mmol/L catechin per mL sample (A) and mmol/L gallic acid per mL sample (B). Results are reported as mean ± SD, data obtained based on P-value<0,05 which was considered statistically significant.

Kombucha Improves Serum Lipid Profile

In this study (figure 3), the average levels of TC (A), LDL (B), and TG levels serum (D), were shown to have a significant decrease and increase in HDL (C) between the KGT and DLP groups (p < 0,05). Furthermore, the Post Hoc LSD test at 5 % revealed that the mean of the DLP group significantly differed compared to the means of the KGT and NC treatment groups.

Kombucha Reduces the Relative Expression of Liver SREBP-1c mRNA

Based on figure 4, the average Fold Change values were highest in the DLP group, followed by the NC group, DLP + KGT 85 mg/kg BW, DLP + KGT 70 mg/kg BW, and DLP + KGT 100 mg/kg BW. The decrease in the relative expression of mRNA SREBP-1c in the livers of rats, which indicated significant differences in Fold Change values among the research groups (p<0,05).

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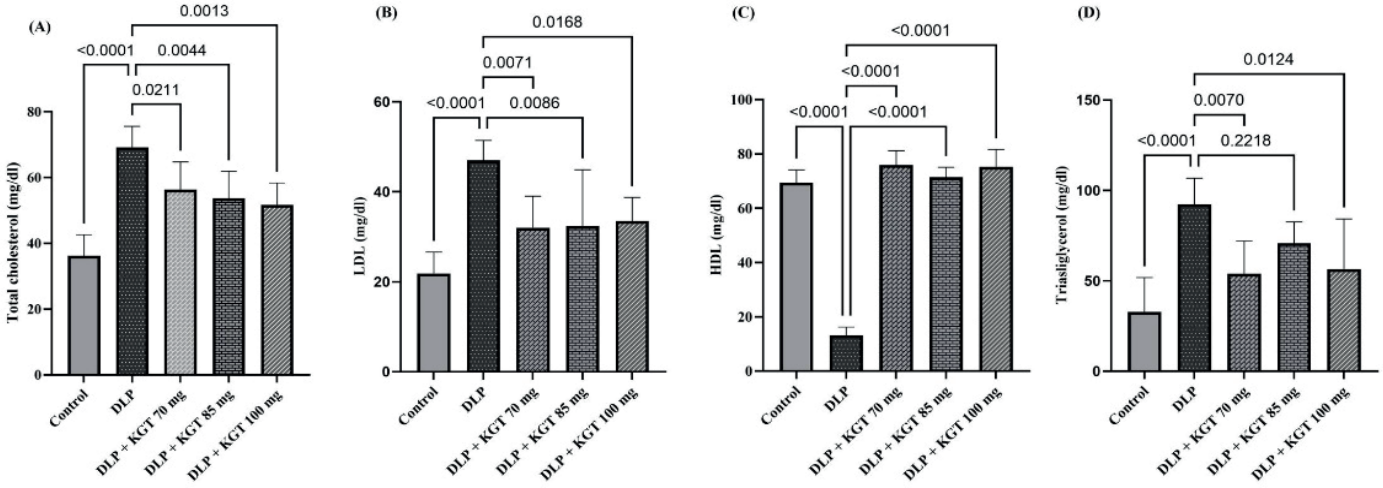

Figure 3. Effect of KGT intervention on serum lipid profile levels in rats

Note: Results are expressed as mean ± SD, data obtained based on P-value<0,05 which is interpreted as statistically significant

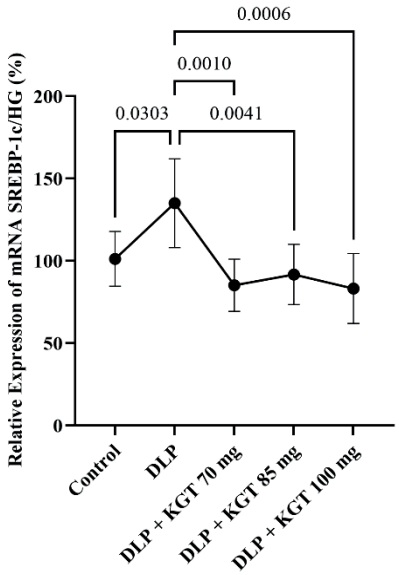

Figure 4. Analysis of SREBP-1c mRNA Expression in Rat Liver Tissue

Note: Data are presented in relative units, with values for the control group (NC) set at 100%. Data are represented as mean ± SD, based on P-value < 0,05 which was considered statistically significant.

DISCUSSION

This study proves an increase in the levels of phenolic compounds and polyphenolic catechins in KGT (Figure 2), this is caused by enzymes produced by bacteria and yeast during the fermentation process, which then break them down into smaller molecules, resulting in an increase in total phenolic compounds and flavonoids. [17] This finding aligns with research using black tea as the base, where water-soluble vitamins such as B1, B12, B6, and vitamin C were found to double in concentration in kombucha black tea after fermentation.[18]

The mechanism of the hypolipidemic effect of kombucha tea is based on the activity of epigallocatechin-3-gallate (EGCG) as a non-competitive inhibitor of pancreatic lipase, which reduces the lipolysis of dietary fats, thereby decreasing the amount of fatty acids entering circulation. As a result, this reduces the formation of LDL, VLDL, and TG while increasing HDL.[19] Additionally, the decrease in TC and TG levels in this study is also associated with the potential presence of probiotics contained in KGT. The mechanism of probiotics is stated to involve the excretion of short chain fatty acids (SCFA) by increasing fatty acid oxidation and increasing intestinal absorption to reduce cholesterol levels. Furthermore, probiotics involved in cholesterol reduction by active probiotic bacteria with Bile Salt Hydrolase (BSH) have been shown to enhance the deconjugation of intraluminal bile acids, resulting in an increased concentration of circulating deconjugated bile salts in humans.This occurs through the secretion of BSH enzymes associated with bile acid deconjugation to emulsify

TG and enhance its hydrolysis to free fatty acids. [20,21]

High Fat Diet (HFD) disrupts the expression of energy metabolism pathways such as AMPK, mTOR, and mitochondrial biogenesis processes. The expression of AMPK and Liver Kinase B1 (LKB1) decreased while mTOR increased significantly.[22] mTORC1 regulates lipid metabolism through phosphorylation of lipin-1, which causes the transcription factor SREBP-1c to bind to lipogenic genes and promote lipogenesis.[23] Disruption of the LKB1/AMPK and mTOR/lipogenesis pathways resulted in a decrease in mitochondrial biogenesis components, such as PGC-1α, NRF1, and Tfam. LKB1 activated AMPK, which could reduce SREBP-1c and increase lipid accumulation in the liver.[24] The decrease in SREBP-1c mRNA aligned with findings that oolong tea increased p-AMPK/AMPK and p-ACC-1/ACC-1, while PPARγ, SREBP-1c, FAS, and SCD-1 decreased. PPAR regulated adipocyte differentiation and lipid metabolism.[25,26] Additionally, the increased concentration of phenolic acids after kombucha fermentation demonstrated anti-obesity of activation of AMPK, NAD+-dependent deacetylases, and PGC1α. The compound EGCG from green tea also modulated energy metabolism through AMPK.[27] Polyphenolic flavonoids present in kombucha could regulate mitochondrial biogenesis in the livers of dyslipidemic rats, and AMPK activation suppressed SREBP-1c by inhibiting mTORC1 and LXRα.[28,29] The limitation of this research is that there has been no identification of the complete microbial composition of the kombucha starter culture (SCOBY) used, where differences in microbial species may have different effects on improving dyslipidemia conditions.

CONCLUSION

This study demonstrates that KGT administered over 14 days can significantly improve serum lipid profile levels and expression of the mRNA transcription factor SREBP-1c in male *Rattus norvegicus* with dyslipidemia. Therefore, there is a need to identify and to review further studies regarding the mechanisms of KGT effects on biomarkers and liver enzyme expression.

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

AUTHORSHIP CONTRIBUTION

Conceptualization: Linda, Lina Lukitasari.
Data curation: Citrawati D.K. Wungu, Sulistiawati.
Formal analysis: Linda, Rahmad Darmawan.
Research: Linda, Lina Lukitasari, Citrawati D.K. Wungu.
Methodology: Sulistiawati, Tri H. Yuliawati.
Project management: Linda, Rahmad Darmawan.
Resources: Ira Humairah, Sulistiawati.
Software: Linda, Ira Humairah.
Supervision: Linda.
Validation: Lina Lukitasari, Citrawati D.K. Wungu.
Display: Linda, Tri H. Yuliawati.
Drafting - original draft: Linda, Lina Lukitasari.
Writing - proofreading and editing: Linda, Lina Lukitasari, Citrawati D.K. Wungu.